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High mobility group box 1 protein, a cue for stem cell recruitment

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Abstract

High mobility group box 1 (HMGB1) is a non-histone protein required to maintain chromatin architecture. Recent observations demonstrated that HMGB1 can also act as a cytokine to regulate different biological processes such as inflammation, cell migration and metastasis. We showed previously that HMGB1 can be released passively by cells that die in a traumatic and unprogrammed way, and can serve a signal of tissue damage. More recently, we showed that HMGB1 can recruit stem cells: HMGB1 induces stem cell transmigration through an endothelial barrier; moreover, when beads containing HMGB1 are implanted into healthy muscle, they recruit stem cells injected into the general circulation. The inflammatory and tissue-regenerating roles of HMGB1 may be strictly interconnected, and are discussed here.

Keywords: Cell migration; Cytokine; Inflammation; Stem cell; Tissue damage; Tissue regeneration

1. Introduction: the role of HMGB1 as a cytokine

High mobility group box 1 (HMGB1) is a nuclear protein that is widely expressed and extremely conserved in mammals. HMGB1 is an architectural protein: it can bend DNA to promote nucleoprotein interactions and facilitate all sorts of DNA transactions. The protein (25 kDa) is structured in three domains: two basic HMG-box domains (A and B) and a long acidic C-terminal tail [1,2]. HMGB1 can interact through its HMG box domains with a wide range of proteins, including the TATA-binding protein (TBP), p53, Hox proteins, the octamer transcription factors (Oct1, Oct2, and Oct4), the steroid receptors (glucocorticoid and estrogen), the recombination activation gene protein RAG1, and several viral proteins [3]. The importance of HMGB1 as interactor of transcription factors is confirmed by the phenotype of *Hmgb1−/−* mice, which have a reduced activity of the glucocorticoid receptors [4].

Recently, several groups have shown that HMGB1 has an extracellular role as a proinflammatory cytokine [5]. Indeed, HMGB1 is a potential therapeutic target for the treatment of sepsis [6] and rheumatoid arthritis [7]. There are two different routes for HMGB1 release into the extracellular milieu: active secretion by activated macrophages and monocytes [8], and passive release from necrotic or damaged cells [9]. HMGB1 does not bind tightly to chromatin in living cells, and readily diffuses into the extracellular space when cells die because of hypoxia, mechanical or thermal damage, or ATP depletion. Conversely, cells that die by apoptosis modify their chromatin so as to bind HMGB1 irreversibly [9]. In this way, HMGB1 release signals cell necrosis, or accidental cell death, as opposed to programmed cell death [10]. The pathway by which HMGB1 is secreted by myeloid cells has been characterized only partially: the protein does not contain a conventional leader sequence and its secretion depends on the relocalization from the nucleus to secretory organelles [11,12].

Abbreviations: DiI, 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate; HMGB1, high mobility group box 1; RAGE, receptor for advanced glycation end products; S.D., standard deviation; TA, *tibialis anterior*; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

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Extracellular HMGB1 acts as a late mediator of inflammation. Kevin Tracey and collaborators detected HMGB1 in the serum of septic patients [8]; anti-HMGB1 antibodies reverse established sepsis [6]. Furthermore, HMGB1 induces the production by macrophages and neutrophils of proinflammatory cytokines, such as TNF, interleukin (IL)-1α and -1β, IL6 and macrophage inflammatory protein 1 (MIP1) [8,13,14]. The treatment of mice with HMGB1 or its B-box domain increased both ileal mucosal permeability to macromolecules and bacterial translocation to mesenteric lymph nodes [15]. On endothelial cells, HMGB1 induces a proinflammatory phenotype, characterized by: (1) upregulation of intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule (VCAM1), (2) production of proinflammatory cytokines, and (3) secretion of regulators of fibrinolysis, tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI1) [16,17].

In addition to its function as a proinflammatory factor, HMGB1 directs the migration of vascular and transformed cells [18]. We showed that HMGB1 released by damaged cells acts as a chemoattractant for vascular smooth muscle cells (SMCs) and fibroblasts, and induces cytoskeleton reorganization and cell migration [19]. HMGB1 induces also tissue invasion and metastasis of cancer cells, most likely through the activation of metalloproteases MMP2 and MMP9 [20,21].

There is considerable interest in identifying the cell surface receptor(s) that mediate HMGB1 functions in cell migration. RAGE, a multiligand receptor of the immunoglobulin superfamily, binds HMGB1 [22] and eventually causes the activation of NF-κB through a reactive oxygen species (ROS) pathway which involves Ras [15]; RAGE also activates the ERK1/2, p38 and SAPK/JNK kinases, as well as the small GTPases Rac and cdc42 [23,24]. Recently, the Toll-like receptors (TLR)-2 and -4 have also been proposed to be involved in cell activation by HMGB1 [25].

Given the multiple effects of HMGB1 in inflammation and tissue remodeling, we investigated the possible role of HMGB1 in the converse but tightly connected process of tissue regeneration. Tissue regeneration often involves the recruitment of stem cells, either locally in the tissue in which they reside, or from anatomically distant compartments (like bone marrow) through the general circulation. Bone marrow-derived stem cells can ingress into different organs like heart, skeletal muscle, brain or liver [26]. For instance, Anderson and co-workers have demonstrated that bone marrow cells can restore cardiac function in damaged myocardium [27].

We set out to investigate whether HMGB1 may activate local stem cells, and whether it can act as a signal in the homing of remotely located stem cells. For these studies, we used primarily the vessel-associated stem cells, or mesoangioblasts. Mesoangioblasts can be isolated from embryonic vessels, and from adult microvessels and muscle, and express CD34, Sca1, Flk1 and MEF2D cellular markers [28]. Mesoangioblasts can differentiate into various mesodermal cell types (including smooth, skeletal and myocardial muscle cells, endothelial cells, and osteoblasts), and when injected into the blood they migrate across the endothelial barrier into the damaged tissue [29]. We demonstrated that HMGB1 activates mesoangioblasts to proliferate, and direct their migration both in vitro and in vivo [30]. Bone marrow-derived stem cells are also attracted by HMGB1, although with a lower efficiency.

2. Effect of HMGB1 on stem cell migration in vitro

To determine whether HMGB1 can chemoattract mesoangioblasts we used Boyden chambers. Fig. 1A shows that HMGB1 has a concentration-dependent effect on mesoangioblast migration. Antibodies against HMGB1 block the migratory response, indicating that the response is not due to a contaminant of the HMGB1 preparation.

We assayed various fragments of HMGB1 to identify the protein segment that promotes mesoangioblast migration. Full-length HMGB1 and a fragment which only lacks the acidic tail (ABbt) are fully active, whereas the individual boxes (box A and box B), or both boxes (box A + B), have no significant chemotactic effect (Fig. 1B). This indicates that the segment from the end of box B to the beginning of the acidic tail (amino acids 165–185) is necessary for the chemotactic effect. Significantly, this segment corresponds to the surface recognized on HMGB1 by the RAGE receptor [18,21]. We previously showed that vascular smooth muscle cells also migrate in response to HMGB1 and to both isolated box A and box B [19]. We presume that the ability of boxes A and B to promote SMC but not mesoangioblast migration corresponds to a specific difference in receptors expressed in these cell types.

Having established that HMGB1 acts as a chemoattractant in vitro, we asked if this protein could also promote the transmigration of stem cells across endothelial barriers. Thus, we compared the effects of HMGB1 on endothelial cells to that a positive control consisting of VEGF. Several studies have shown that VEGF induces profound cytoskeletal reorganization of endothelial cells, characterized by the formation of transcytoplasmic stress fibers [31]. Furthermore, treatment with VEGF destroys the adherens junctions between the endothelial cells, which are important to maintain the endothelial barrier. After stimulation with HMGB1 for 5–30 min endothelial cells were fixed and actin filaments were labeled with fluorescein-conjugated phalloidin. Stress fibers were formed to a similar extent as with VEGF, although the effect appeared less long-lived (Fig. 1C).

We also investigated the ability of mesoangioblasts to migrate through an endothelial monolayer overgrown on the filter that separates the compartments in a classical cell

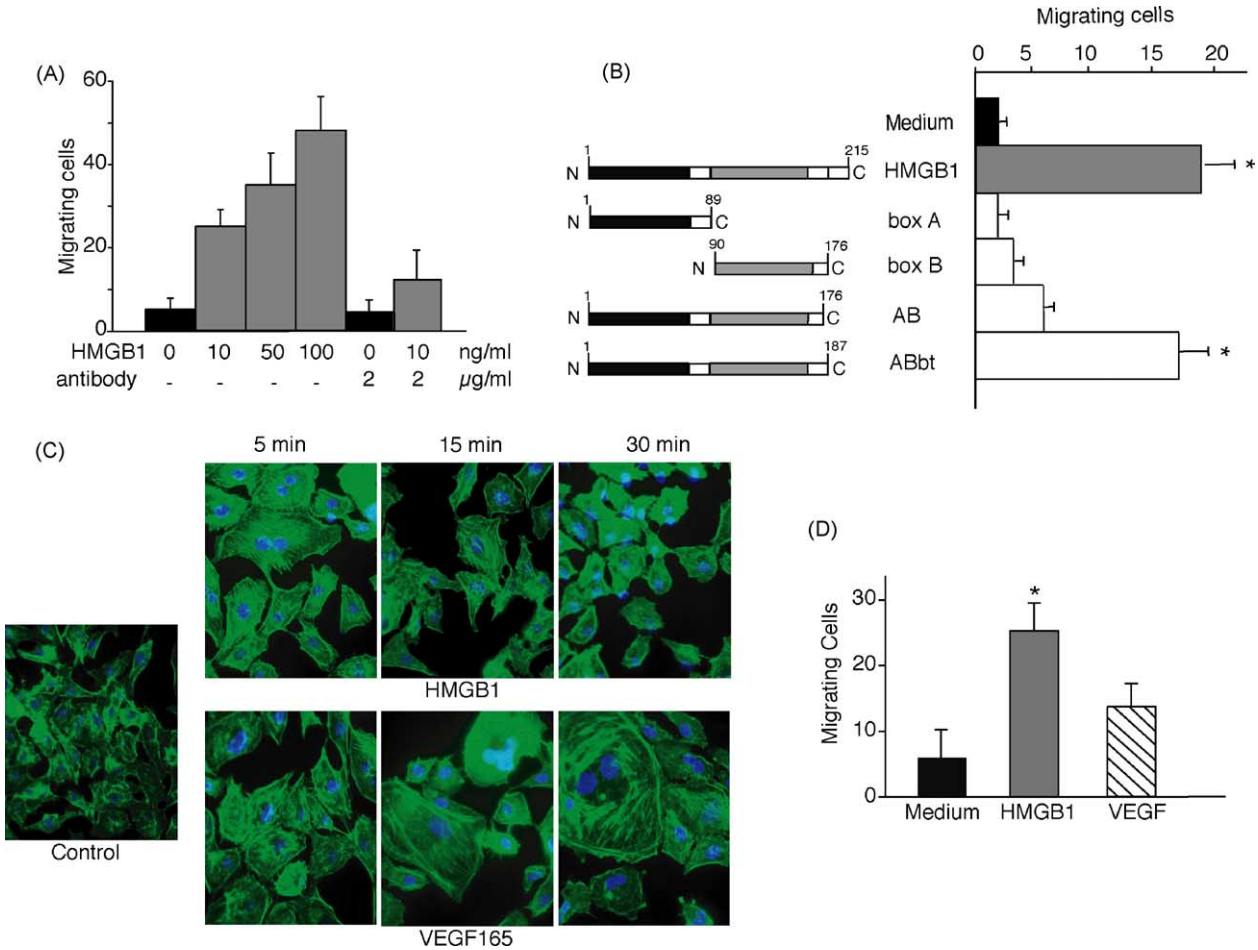

Fig. 1. HMGB1 has chemotactic activity on mesoangioblasts, and promotes their transit across endothelial monolayers. (A) Mesoangioblasts (D16 clone) were subjected to chemotaxis assays with 10, 50, or 100 ng/ml HMGB1. Data represent the average ± S.D. of four experiments performed in duplicate; the effect of increasing HMGB1 concentrations is highly significant ($P < 0.001$ in ANOVA analysis). Addition of anti-HMGB1 antibodies recognizing the peptides 166–181 significantly reduced the chemotactic response ($P < 0.05$ in comparison to the sample without antibody). (B) Chemotactic activity on D16 mesoangioblasts of various HMGB1 fragments (full length HMGB1, boxes A and B, the didomain AB, and ABbt fragment corresponding to tailless HMGB1, all at 10 ng/ml). ABbt has a chemotactic effect comparable with full length HMGB1 ($P < 0.05$ of proteins vs. medium alone). Bars represent the average ± S.D. of three experiments performed in duplicate. (C) Bovine primary endothelial cells (BAECs) grown to confluence on glass coverslips were exposed to HMGB1 or VEGF and stained with fluorescein-labeled phalloidin to visualize actin fibers. Both treatments determined the formation of stress fibers, and the separation of cells from each other. (D) HMGB1 induces the transit of mesoangioblasts through an endothelial monolayer. D16 mesoangioblasts were placed in the upper compartment of Boyden apparatuses; the compartments were separated by a confluent endothelial cell monolayer grown on polycarbonate filters; the lower chambers contained RPMI alone (medium), RPMI plus 100 ng/ml HMGB1 or RPMI plus 10 ng/ml VEGF. Bars represent the average ± S.D. of three experiments performed in duplicate; the asterisk indicates statistical significance ($P < 0.05$).

migration assay. In the presence of 100 ng/ml HMGB1 in the lower compartment, a significant number of mesoangioblasts migrated across the endothelial layer and the filter, and the effect was even more pronounced than in the presence of 20 ng/ml VEGF (Fig. 1D).

Taken together, these findings support the idea that HMGB1 can play a role in stem cell attraction.

3. Effect of HMGB1 on stem cell migration in vivo

Having established in vitro a role for HMGB1 as a stem cell chemoattractant, we decided to assess its ability direct migration in vivo. Heparin–sepharose beads were loaded with HMGB1 at the concentration of 3 μg/ml and then injected into the *tibialis anterior* (TA) muscles of mice. Mesoangioblasts, transduced by a lentiviral vector expressing nuclear LacZ to facilitate recognition, were injected 30 min later through the femoral artery. The mice were sacrificed after 24 h, and we inspected TA muscles by immunohistochemistry for evidence of mesoangioblast ingress. The sections were stained with X-gal and blue cells were counted using computer-assisted imaging techniques. We found mesoangioblasts in TA muscles of mice treated with HMGB1-loaded beads; no blue cells were found in TA muscles of mice treated with empty heparin–sepharose beads (Fig. 2A). Inflammation, which is also caused by the injection of HMGB1, might have played a

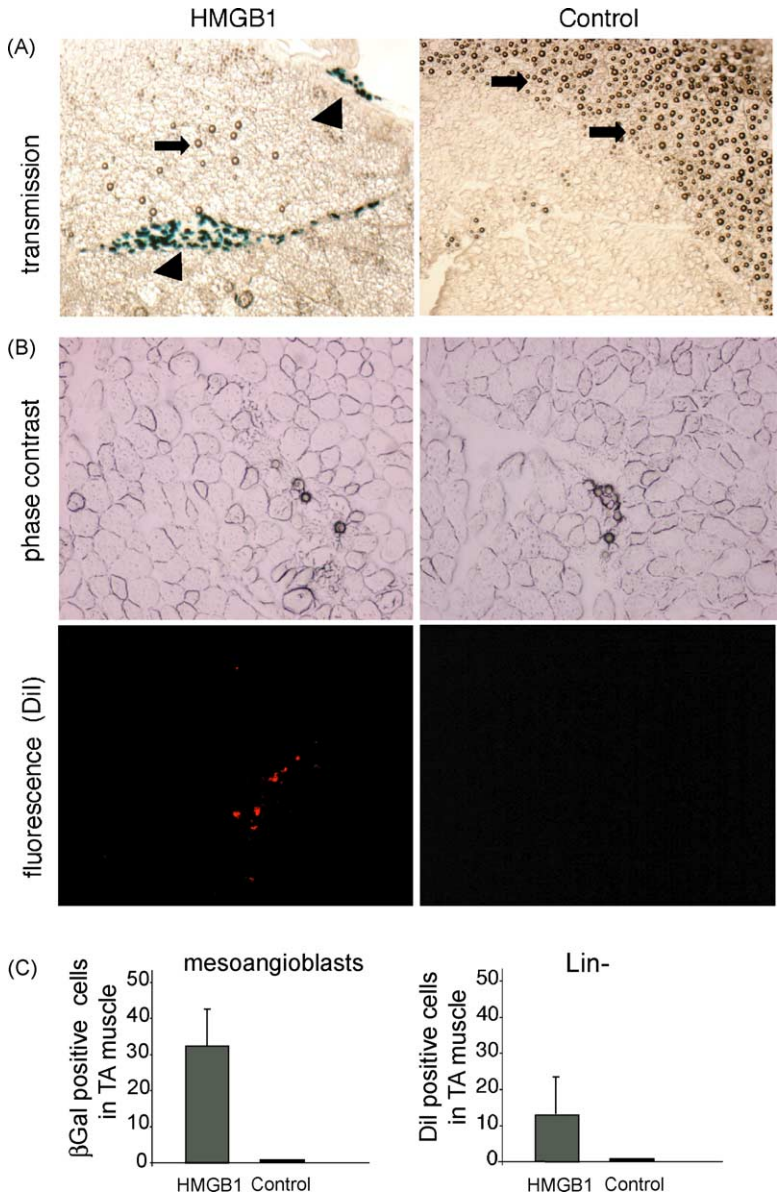

Fig. 2. HMGB1 attracts mesoangioblasts in vivo. D16 mesangioblast were first transduced with a lentiviral vector encoding nuclear LacZ, whereas lin$^-$ cells were pre-loaded with the vital fluorescent label DiI. Cells (4×10^5/animal) were then injected through the femoral artery of mice where heparin–sepharose beads (either loaded with HMGB1 or unloaded) had been injected in TA muscles. Mice were then sacrificed after 24 h. (A) Sections from TA muscle injected with HMGB1-loaded and control beads. Arrows indicate the beads. Mesoangioblasts (arrowheads) are stained with X-gal and appear blue. (B) Section from TA muscle injected with HMGB1-loaded and control beads. Lin$^-$ cells are identified by the red fluorescence of DiI. (C) Number of migrating cells in TA muscles of mice treated with HMGB1-loaded beads (grey bar; $n = 2$) or control beads co-injected with 1 μg LPS ($n = 3$; black bar).

confounding role in this experiment; we therefore injected empty heparin–sepharose beads together with bacterial lipopolysaccharide (LPS), an inflammatory agent. Again, we found no blue cells in the vicinity of beads in TA muscles.

We also analyzed whether HMGB1 was able to attract other types of stem cells. We purified lin$^-$ hematopoietic stem cells from mouse bone marrow, and injected them in mice where HMGB1-loaded beads had been implanted in TA muscles. Before injection the stem cells were loaded with the vital fluorescent dye DiI, and DiI-positive were counted in sections of the TA muscle where beads were also present. Positive cells were found in TA muscles of mice treated with HMGB1, and no cells in muscles where empty beads had been injected (Fig. 2B). However, the number of migrating hematopoietic stem cells was lower in comparison to migrating mesoangioblasts (Fig. 2C). The lower ability of hematopoietic stem cells to respond to HMGB1 in this assay may be due to various factors: a reduced ability to detect HMGB1 via surface receptors, a reduced capacity to traverse endothelial barriers, or a reduced capacity to migrate within muscle tissue. Nonetheless, our in vivo observations clearly suggest that HMGB1 can also attract bone marrow-derived stem cells.

4. Future perspectives

In the past few years, several reports have suggested the potential therapeutic role of stem cells in tissue regeneration. Stem cells can transit through the circulation and gain access to organs as heart, brain, muscle and liver. Homing signals resulting from local damage are expected to direct the migration of stem cells to specific sites; other factors, including the extracellular matrix microenvironment, the nature of the local stimulus and the interplay between the differentiated cells in the tissue and the stem cells can also play key roles in determining stem cell recruitment.

Recently, some factors that are implicated in the migration of stem cells have been identified. One such factor, transforming growth factor alpha (TGF-α), is involved in the proliferation and migration of neural stem cells (NSC) within the brain. When infused into the forebrain of rats with lesions induced by 6-hydroxydopamine, not only TGF-α induced the proliferation of endogenous NCS, but it also diverted stem cell migration toward the infusion site [32]. Another report showed that stromal cell-derived factor 1 (SDF-1) and hepatocyte growth factor (HGF) increase the homing of human $CD34^+$ stem cells to the liver [33]. Cardiomyocytes overexpressing TNF are able to enhance the migration of embryonic stem cells in vitro [34]. Finally, insulin-like growth factor 1 (IGF-1) recruits bone marrow stem cells to damaged muscle tissue [35].

Our studies indicate that HMGB1 is an important player in the migration of stem cells. Our experiments were performed in muscle and used primarily the vessel-associated mesoangioblasts, simply because this experimental setting is exquisitely suited for in vivo studies [29]. We may expect that several other types of stem cells will also be responsive to HMGB1; indeed, HMGB1 can also recruit bone marrow-derived stem cells.

Our in vivo experiments were performed by implanting HMGB1-loaded beads in muscle tissue that was otherwise normal and healthy. This model is intended to replicate a situation where HMGB1 is released passively in the neighboring tissue by mechanically damaged or necrotic cells, for example as a consequence of impact or burns, and HMGB1 itself signals tissue damage. Importantly, we have also shown that the RAGE receptor plays an important role in the stem cell response to HMGB1. We should not forget, however, that damaged tissue triggers inflammatory responses (at least in part also via HMGB1 release); inflammation causes the recruitment of neutrophils, monocytes, and macrophages, which in turn secrete a large number of other cytokines, chemokines and metalloproteases (they also secrete a multiply acetylated form of HMGB1). Inflammatory cells create a first line of defense against microorganisms that are likely to invade the tissue following the damage, but also cause local damage to the inflamed tissue, and kill and eliminate resident cells [36]. However, by partially destroying the tissue they infiltrate, inflammatory cells create a niche where stem cells can engraft and participate in tissue remodeling and healing. It is most likely that inflammatory cells will be able to attract stem cells in a variety of ways, using a number of different chemoattractants. We have shown that HMGB1 and its receptor RAGE can play an important role, sufficient in itself for stem cell recruitment, but we certainly do not expect them to be the only ligand/receptor pair implicated in processes where stem cells are recruited to heal the damaged tissue. In fact, HMGB1 can have an indirect role as well, by stimulating the production of proinflammatory cytokines and chemokines, such as TNF, IL-1, IL-8 and MIP1s.

The coincidence between the inflammatory role of HMGB1 and its ability to induce recruitment of mesoangioblasts is interesting from both a basic and an applied point of view. At a basic level, the concept that tissue damage is a source of signals that elicit at the same time inflammation and the recruitment of stem cells is important. From a therapeutic viewpoint, the use as a stem cell chemoattractant of a molecule that causes sepsis when delivered systemically is obviously of some concern. We note however that the systemic effects become prevalent at a protein amount about two orders of magnitude higher than the amount we used locally in TA muscle. Moreover, we did not try to optimize the amount of HMGB1 used to effect stem cell recruitment, and it is possible that much lower amounts would also be efficacious in a clinical setting.

Our studies also need some extension in an altogether different direction. As already discussed, the implantation of HMGB1-loaded beads in muscle mimics the release of HMGB1 from necrotic or damaged cells; we then assayed the homing of stem cells from circulation to muscle. It is well known, however, that several organs contain a pool of resident stem cells. A very important question is whether HMGB1 induces the activation of these resident stem cells to proliferate and differentiate, ultimately replacing the cells that have died. For instance, basic fibroblast growth factor (FGF2), epidermal growth factor (EGF), and bone morphogenetic protein-4 (BMP4) can induce differentiation of NSC into neurons [37]. The ability of stem cells to regenerate injured tissue represents a promising therapeutic strategy. It will be interesting to see whether HMGB1 can be used to promote such tissue regeneration, preferably without the need for stem cell explant, in vivo expansion and re-injection.

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